CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74787

CORRESPONDENCE

ANDA 74-787

Zenith Goldline Pharmaceuticals Inc.
Attention: Robert Monaghan
140 Legrand Avenue
Northvale NJ 07647

SEP 10 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg, 300 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

/S/ Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-787

Zenith Goldline Pharmaceuticals, Inc. FEB 9 1996
Attention: Robert Monaghan
140 Legrand Avenue
Northvale NJ 07647

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg, 300 mg

DATE OF APPLICATION: November 14, 1995

DATE OF RECEIPT: November 20, 1995

We also refer to your correspondence dated January 25, 1996.

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Tim Ames
Consumer Safety Officer
(301) 594-0310

Sincerely yours,

/S/ 2/9/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-787

Zenith Goldline Pharmaceutical, Inc.
Attention: Robert Monaghan
140 Legrand Avenue
Northvale, NJ 07647

JUL 3 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated November 14, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. For components and composition:

a. Please indicate the quantity and limits of Purified Water, USP used in the composition of the drug product.

b. Please separately list the components for

in the components and composition section.

c. "The total average tablet weight depending upon coating conditions" and "a % excess of color additives

is prepared to compensate for manufacturing loss" stated in the composition and batch records are unacceptable. Please justify and submit reasonable limits for total tablet weight and color additives in the composition section and batch records.

2. Regarding Active Ingredient:

a DMF is deficient and the holder has been notified by letter. It is necessary that all the deficiencies be corrected before this application can be approved.

b. The Certificate of Analysis for Labetalol Hydrochloride from was incomplete. Please include Organic Volatile Impurities testing as per USP 23 requirements.

c. We note that "reduction in Standard and Sample concentration from µg/mL of USP method to µg/mL" was stated in your modified assay method. Please comment and justify.

3. Submit FDA color certificates for D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake and FD&C Blue No. 6 Aluminum Lake.

4. The submission fails to provide a complete formula card and satisfactory batch records. In this regard:

a. Submit the revised formula card (see comments 1.a-c).

b. Indicate and submit the specifications for blend analysis (top, middle and bottom portions of final blend) prior to tableting in the test, blank and proposed batch records.

c. Specifications for tablet compression including description of equipment, die, operating speed and compression parameters should be included.

d. The coating process should include in-process control of moisture and average weight. The blank batch record for future production should be revised accordingly.

e. What controls are used to evaluate the suitability of the cores before coating. How are the cores stored until coating? Please discuss and submit any available supporting data.

f. Packaging and labeling reconciliation information should be included in the proposed (blank) batch records.

5. Your application fails to present complete descriptions of the container/closure systems. In that regard:

a Submit actual test results to demonstrate that

resins meet the current USP 23 requirements for plastic containers.

b. Submit the actual torque test for cap removal covering the 500's package size for each strength.

6. We note that there are no packaging batch records for the 500's package size for each strength of Labetalol Tablets on Lots ND-242, ND-241, and ND-243. We require that the ANDA test batches be packaged entirely. Refer to OGD Industry Letter dated November 8, 1991, and OGD Policy and Procedure Guide #41-95 dated February 8, 1995. Please provide justification for the partial packaging and a protocol to support partial packaging of the test batches.

7. Regarding finished product:

   a. The Certificate of Analysis for the finished product is incomplete. Batch size, date of manufacture, the source of active ingredient, manufacturing procedure (e.g., pilot or production batch), and manufacturing site should be included.

   b. The stability-indicating assay method submitted in Section XVI of original submission is incomplete. Please submit in percentages the assay results of the active ingredient and degradation products under various stress conditions in tabular form.

8. Your application fails to submit satisfactory stability data. In this regard:

   a. Composition [see comments 1.(a-c)] of the drug product must be included.

   b. Please provide more specific information regarding "Physical evaluation" (e.g., color, odor, etc.).

B. Labeling Deficiencies:

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this

letter will be considered a **MAJOR** amendment and should be so designated in your cover letter. You will be notified in a separate letter of deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Labeling Enclosure

Zenith Goldline
PHARMACEUTICALS

Noted.

NEW CORRESP
NC +
FA

Regulatory Affairs

Via Federal Express and Telefax (Cover Letter only) to (301)827-4337

June 5, 1998

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
JUN 0 8 1998
GENERIC DRUGS

FACSIMILE AMENDMENT

RE: Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg, and 300 mg
ANDA 74-787

Dear Mr. Sporn:

Reference is made to the Agency's Facsimile Amendment letter dated May 12, 1998 (copy attached), concerning our Abbreviated New Drug Application for the above referenced product. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your correspondence. As stated in your correspondence, this response should be considered a FACSIMILE AMENDMENT, as it is submitted within 30 days of receipt of the Agency's letter.

In response to the Agency's comments, we submit the following:

A. CHEMISTRY DEFICIENCIES

1. *The Certificate of Analysis for batch ND-398 was submitted on September 26, 1997 in support of the theoretical coating weight gain (range). The dissolution results are within the specified limit. Please submit the batch record and 3 months accelerated stability data for lot ND-398 since the 200 mg strength is used for your bioequivalence study batch.*

Response:
Please refer to Attachment 1 of this amendment, in which we have provided copies of the batch record and 3 months accelerated stability data for Labetalol HCl Tablets USP, 200 mg, Batch No. ND-398. The 3 months accelerated stability data for the finished product in containers of 100 (CRC and non-CRC) and 1000 tablets meet specifications satisfactorily, and further support a tentative 24 month expiry period.

2. *We note that the test results for containers and containers have been submitted in the original submission and the September 26, 1997 amendment. We also note resin and resin were used to manufacture the 100's, 500's, and 1000's package sizes. It is necessary to demonstrate the interchangeability of each resin by compendial testing. Please submit actual test results to demonstrate that and resins meet the current USP 23 requirements for plastics for container. A Certificate of Analysis from the manufacturer is also acceptable.*

Response:
Please refer to Attachment 2, in which we have provided a copy of the USP 23 monograph <661> for polyethylene containers, as well as a copy of Table 8 (page 40) from FDA's Draft Guidance entitled, "*Submission of Documentation in Drug Applications for Container Closure Systems Used for the Packaging of Human Drugs and Biologics, June 1997*". These references support Zenith Goldline's assertion that testing of the unformed resin component is unnecessary for inclusion in this application, and not part of the official compendium. Specifically, the USP 23 <661> monograph for Containers states,

> *"Where dry oral dosage forms, not meant for constitution into solution, are intended to be packaged in a container defined in the section* ***Polyethylene Containers****, the requirements given in that section are to be met."*

The monograph for Polyethylene Containers specifies that compendial testing consists of Multiple Internal Reflectance, Thermal Analysis, Light Transmission, Water Vapor Permeation, and Heavy Metals and Nonvolatile Residue. As the Agency is aware, this data has already been submitted for all container sizes. The compendial monograph does not specify testing to be done on the unformed resin.

The FDA's Draft Guidance entitled, "*Submission of Documentation in Drug Applications for Container Closure Systems Used for the Packaging of Human Drugs and Biologics, June 1997*" further supports this position. Specifically, Table 8 (page 40), footnote "b" states,

> *"Characterization tests for plastics should be performed on packaging components, not on the unformed resins."*

Thus, we request that the Agency maintain their position as expressed in the draft guidance, and in accord with the official compendium.

3. *The master batch record for the 100 mg product appears to include variable process settings on page 35. However, on page 36 the in-process control for granulation end-point is specified for one process setting only. Please revise page 35 to specify one process setting based on your executed batch record. Please revise the master batch records for the 200 mg and 300 mg products also.*

Response:
We acknowledge the discrepancy in the master batch records (MF/SOIs), in which one step of the granulation process includes

We have revised Steps

4. *Please submit the drug product release specifications to include the revised description of the drug product for each strength.*

Response:
As instructed, we have revised our release specifications for the in-process cores and finished product, as well as for stability testing, to provide for the new product descriptions. These are provided in Attachment 4 of this amendment. Please be assured that no other changes have been made to either the test methods or limits, which remain identical to those submitted in our original application.

B. BIOEQUIVALENCY COMMENTS

1. *The Division of Bioequivalence has completed its review and has no further questions at this time.*

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in the USP 23.

Please note that the bioequivalency comments provided in the earlier communication (9/10/96) are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Response:
We understand that there are no outstanding bioequivalence issues at this time. We have incorporated the dissolution testing into our stability and quality control programs as specified in the USP 23. A copy of our current Stability Specification/Analysis report is provided in Attachment 4. Zenith Goldline acknowledges that the bioequivalence data may be subject to further review based on scientific or regulatory issues in the future.

This completes our Facsimile Amendment response to the Agency's comments of May 12, 1998. We trust that all outstanding deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director of State, Federal and
International Regulatory Affairs

/sb
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Attachments

Zenith Goldline
PHARMACEUTICALS

September 26, 1997

ORIG AMENDMENT

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

RE: Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg
ANDA 74-787

Dear Mr. Sporn:

Reference is made to the Agency's letter dated July 3, 1996 (copy attached), concerning our abbreviated new drug application for the above referenced product. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your "not approvable" letter. Although this amendment appears large in size, many of the attachments were previously submitted in our original ANDA filing, and are included here to facilitate review. As stated in your letter, this response should be considered a MAJOR amendment.

In response to your comments, we submit the following:

A. CHEMISTRY DEFICIENCIES

1. For components and composition:

a. Please indicate the quantity and limits of Purified Water USP used in the composition of the drug product.

Response:
Purified Water is utilized in of the manufacturing process of Labetalol Hydrochloride Tablets USP,
During the . Purified Water is used as a

100 mg tablet: NMT % of mg (upper wt. limit) = mg of water
200 mg tablet: NMT % of mg (upper wt. limit) = mg of water
300 mg tablet: NMT % of mg (upper wt. limit) = mg of water

We have revised our component and composition statements to incorporate the moisture limits, and these documents have been provided in Section 1 of this amendment.

b. Please separately list the components for in the components and composition section.

Response:
We have revised our component and composition statements to separately list the components for These are provided in Section 1 of this amendment.

c. "The total average tablet weight variable depending upon coating conditions" and "a % excess of color additives is prepared to compensate for manufacturing loss" stated in the composition and batch records are unacceptable. Please justify and submit reasonable limits for total tablet weight and color additives in the composition section and batch records.

Response:
With regard to total average tablet weight: In accordance with the Agency's request, we have deleted the statement, from our composition statement and Master Formula/Standard Operating Instructions (MF/SOIs), and have established theoretical weight gain limits and average weight ranges as in-process controls for the finished product as follows:

Dosage Strength	Theoretical Weight Gain (Range)	Average Weight (Range)	Actual Weight Gain in Test Batch
100 mg	4 mg (mg)	154 mg (mg)	mg (ND-242)
200 mg	8 mg (mg)	308 mg (mg)	mg (ND-241) mg (ND-398)
300 mg	12 mg (mg)	462 mg (mg)	mg (ND-243)

We acknowledge that the actual weight gain of 4.7 mg for our 200 mg exhibit batch (ND-241) falls below the newly established range of mg. Even at this low value, however, batch ND-241 exhibits dissolution results well within the specified limit (see Certificate of Analysis provided in Section 10 of this amendment). Nonetheless, since the actual weight gain of exhibit batch ND-241 did fall below the newly established range, we deemed it prudent to manufacture a second 200 mg batch, ND-398, to obtain a film coating thickness which is within the acceptable limit. As indicated in the table above, the actual weight gain of 9.8 mg for batch ND-398 is within the specified limit of 6-10 mg. This value is representative of the higher end of the range and, as is the case for batch ND-241 which is considerably lower, the dissolution results for batch ND-398 are well within the specified limit. The Certificate of Analysis for batch ND-398 can be found in Section 10 of this amendment.

Please refer to Sections 1 and 2 of this amendment, in which we have provided our composition statement and scale-up MF/SOIs (specifically, the Aqueous Film Coating Data Form) revised to reflect the new weight limits.

With Regard to Excess of Color Components: In response to the Agency's comment, we have deleted the statement, from our MF/SOIs. Instead, we have revised our MF/SOIs (specifically, the Master Formula Card) to specify the maximum quantity of color component necessary to attain the upper coating limit, taking into consideration the wastes accrued during setup, calibration, and flow rate adjustments which are essential to the film coating process. From our experience, this extra is calculated at %. Please refer to Section 2 of this amendment.

In addition, it is important to note that our MF/SOIs for each dosage strength do specify the approximate amount of film coating suspension to be used for each sub-batch to achieve the desirable attributes. Any suspension remaining after the coating process has been completed is measured, recorded in the appropriate space on the revised Aqueous Film Coating Data Form, and discarded in accordance with our standard operating procedures.

2. *Regarding Active Ingredient:*

   a. *DMF is deficient and the holder has been notified by letter. It is necessary that all the deficiencies be corrected before this application can be approved.*

Response:
Zenith Goldline acknowledges that all DMF deficiencies must be corrected prior to approval of our application. Please note that our proposed source of Labetalol Hydrochloride drug substance, responded to the deficiencies pertaining to DMF on September 30, 1996. Section 3 of this amendment contains a copy of the cover letter which accompanied deficiency response.

   b. *The Certificate of Analysis for Labetalol Hydrochloride from was incomplete. Please include Organic Volatile Impurities testing as per USP 23 requirements.*

Response:
This comment refers to the Certificate of Analysis for Labetalol Hydrochloride USP, Zenith Lot #PD-0937 batch #10323) included on pages 112-113 of our original application. There is no potential for drug substance to contain organic volatile impurities, however, their Certificate of Analysis inadvertently omitted a statement to that effect. (Please note that the Certificate of Analysis for batch #10288, provided on pages 110-111 of our original application, does provide the OVI statement.) Accordingly, the Certificate of Analysis for batch #10323 has been revised by Procos to address organic volatile impurities. The revised Certificate of Analysis is provided in Section 3 for your review.

   c. *We note that "reduction in Standard and Sample concentration from µg/mL of USP method to µg/mL" was stated in your modified assay method. Please comment and justify.*

Response:
Please refer to Section 4 of this amendment, in which we have provided a report entitled, *"Modification to the USP Methods: Validation of the Stability Indicating Assay"* (See Part I), and related *Crossover Study Report #LAB-052896*. These reports provide detailed justification and validation for our modified USP Assay Method. For ease of review, Section 4 also contains a copy of our validation report entitled, *"Validation of Analytical Methods USP 23 (Modified) and LAB-LC-DEG-1 for Labetalol HCl Tablets USP and Drug*

Substance", which was previously submitted in our original ANDA. We trust that this information will satisfy the Agency's concern.

3. *Submit FDA color certificates for D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake.*

Response:
Please note that the Lakes listed in the Agency's comment refer to the components in the composition of Yellow (D&C Yellow No. 10 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake) and Green (D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake). the manufacturer of the film coatings, provides a statement in each of their Product Specification sheets certifying that the ingredients used in these products *"meet the requirements listed in the USP, FCC, or 21 CFR for the intended use in Drugs and Cosmetics"*. Since the requirement for FDA Certification is a regulation set forth under 21 CFR, this statement confirms that the ingredients used in the products, e.g., the Lakes, are FDA certified. Based on regulatory statement, therefore, it is our opinion that obtaining FDA certificates for the Lakes found in their products is unnecessary. The Product Specification sheets for Yellow and Green were provided on pages 265 and 273 of our original application, however, for ease of review, we have included duplicates in Section 5 of this amendment.

4. *The submission fails to provide a complete formula card and satisfactory batch records. In this regard:*

   a. *Submit the revised formula card (see Comments 1.a.-c.).*

Response:
As per Comments 1.a.-c., we have revised our Master Formula Cards to delete the aforementioned statements regarding average tablet weights and color excess, as well as to specify the individual components and maximum quantity of color component necessary for coating. However, please note that the newly established limits for moisture and tablet weight range do not appear on the revised Master Formula Cards. The reason for this is that it is not Zenith Goldline's policy to include this type of information on our Master Formula Cards. Rather, please be assured that these data do appear on the revised Aqueous Film Coating Data Form, which is indeed part of the MF/SOI, located in Section 2 of this amendment.

b. Indicate and submit the specifications for blend analysis (top, middle and bottom portions of final blend) prior to tableting in the test, blank and proposed batch records.

Response:
The specifications indicating sampling positions for blend analysis are governed under Zenith Goldline's Standard Operating Procedure #QA-1388, entitled, *"QA Sampling of Blend Uniformity"*. This SOP provides instructions for blend sampling with corresponding diagrams of various blenders used in manufacturing. The diagram indicating the sampling locations for the V-Blender, (the blender utilized in test batch manufacture and specified for commercial production) has been extracted from this Standard Operating Procedure and included in Section 6 of this amendment.

The results of the blend analysis are recorded on the *"In-Process Blend Specification/Analysis Report"*, which specifies each sampling location and its individual result, as well as mean data. This analytical report is included as part of the permanent batch record for each product. In-Process Blend Specification/Analysis Reports for our test batches of Labetalol HCl Tablets USP (100 mg/ND-242, 200 mg/ND-241, and 300 mg/ND-243), were provided on pages 767-769 of our original application, however, for ease of review, duplicates are provided in Section 6 of this amendment.

c. Specifications for tablet compression including description of equipment, die, operating speed and compression parameters should be included.

Response:
Please refer to Step of our revised MF/SOIs for tablet cores, located in Section 2 of this amendment. This step provides

Additionally, we would like to take this opportunity to provide for a minor change in the existing code imprint. Specifically, we will, in future batches, discontinue the use of the "Zenith" logo in favor of the current "Ivax" logo, which appears on the tablet as a symbol, "⧖". Thus, the logo description in Step of our updated MF/SOIs for tablet cores has been appropriately modified. Please be assured that no other changes have been made regarding punch/die size, shape, bisect, etc. At such time that the first annual report is filed, in accordance with 21 CFR §314.70(d)(9), we will provide the Agency

with a comparative dissolution profile and monitoring will continue throughout our ongoing stability program.

d. *The coating process should include in-process control of moisture and average weight. The blank batch record for future production should be revised accordingly.*

Response:
As requested, we have revised our blank batch records (MF/SOIs) for each dosage strength to include in-process controls for both moisture content and average tablet weight. The moisture limit is specified as not more than %; the Loss on Drying will be performed by Karl Fisher method, and the results will be recorded in the applicable space on the "Aqueous Film Coating Data Form" portion of each MF/SOI (Section 2 of this amendment).

With regard to average tablet weight, we have revised our MF/SOIs to provide specifications for theoretical weight gain and average weight ranges during the process. These provisions are also contained in the "Aqueous Film Coating Data Form" portion of each MF/SOI (Section 2 of this amendment). Please refer to our response to Comment #1(c) for the complete details regarding these in-process weight controls.

e. *What controls are used to evaluate the suitability of the cores before coating? How are the cores stored until coating? Please discuss and submit any available supporting data.*

Response:
Please note that complete information concerning the analysis and holding of the tablet cores is provided in Section XII.2. (In-Process Controls) of our original ANDA submission. As indicated on Page 744, tablet core samples are collected at evenly spaced intervals throughout the compression run, and, during validation, are then tested for content uniformity and dissolution. These test results are documented in an In-Process Specification/Analysis Report, copies of which are found on Pages 750, 752, and 754 of our original ANDA submission. For ease of review, we have included duplicates of these documents, as well as copies of the actual test data for the exhibit batches (ANDA submission Pages 770-772) in Section 7 of this amendment.

Once validated, as Page 748 specifies, routine in-process tablet core testing consisting of weight variation, thickness, hardness, friability, and yield determinations will be conducted and documented as part of each batch record.

As indicated in our exhibit batch records (Step , scale-up MF/SOIs (Step , and ANDA Page 745, the tablet cores are held in double polyethylene bag-lined containers until coating. A letter from the manufacturer of the polyethylene bags, can be found on Page 746 of our ANDA filing, and provides certification that the materials used in the manufacture of their polyethylene resin complies with FDA requirements. For ease of review, we have included a duplicate of this letter in Section 7 of this amendment.

Information pertaining to tablet core hold times is covered by Zenith's SOP entitled, *"Manufacturing Time Limitations for Production"*, which is summarized on Pages 744-745 of our original ANDA filing. As this section indicates, the manufacturing cycle, from the initial date of the blending of the active ingredient to the completion of the finished product, is targeted not to exceed 45 days. Products which exceed a production time of 45 days must be supported by stability indicating testing prior to release in order to support the expiration date. This testing will consist of stability indicating assay, plus blend content uniformity, visual inspection for agglomerations, particle size analysis, and moisture testing, where applicable. Batches which exceed 90 days in processing will be rejected and destroyed.

f. Packaging and labeling reconciliation information should be included in the proposed (blank) batch records.

Response:
Please refer to Section 8 of this amendment, in which we have provided example copies (blank) of our packaging and labeling reconciliation forms which are routinely completed and attached to every batch record. Please note that complete packaging and labeling reconciliation data for the three exhibit batches of Labetalol Hydrochloride Tablets USP were included in our original ANDA submission as part of each batch record.

5. *Your application fails to present complete descriptions of the container/closure systems. In that regard:*

a. Submit actual test results to demonstrate that and resins meet the current USP 23 requirements for plastic containers.

Response:
Please note that test data demonstrating conformance of the resin bottles) to USP 23 <661> requirements for polyethylene containers are included in Section XIV, Pages 789-815, of our original ANDA submission. These data include analytical reports for the 60cc, 100cc, 150cc,

and 400cc bottles. However, as we were preparing this amendment, we noticed that the analytical report for the 300cc bottle was inadvertently omitted from this section of the ANDA. We apologize for any inconvenience this may have caused, and are submitting the report for the 300cc bottle, along with duplicate copies of the analytical reports for the 60cc, 100cc, 150cc, and 400cc containers, in Section 9 of this amendment.

In reference to the resin bottles), we acknowledge that the analytical reports for 625cc and 750cc bottles, provided on Pages 824-845 of our original ANDA submission, pertain to USP22/21 test requirements. Therefore, we are amending our application to provide test data demonstrating conformance of the resin to the current USP 23 <661> requirements for plastic containers. Please refer to the analytical reports for the 625cc and 750cc containers located in Section 9 of this amendment.

b. *Submit the actual torque test for cap removal covering the 500's package size for each strength.*

Response:
Torque testing for cap removal on the 500's package size was not provided in our application because this container/closure system was not packaged. Please refer to our following response to Comment No. 6 for a full justification of our packaging scheme.

6. *We note that there are no packaging batch records for the 500's package size for each strength of Labetalol Tablets on Lots ND-242, ND-241 and ND-243. We require that the ANDA test batches be packaged entirely. Refer to OGD Industry Letter dated November 8, 1991, and OGD Policy and Procedure Guide #41-95 dated February 8, 1995. Please provide justification for the partial packaging and a protocol to support partial packaging of the test batches.*

Response:
Please be assured that our ANDA test batches, ND-242 (100 mg), ND-241 (200 mg) and ND-243 (300 mg) were indeed packaged in their entirety in accordance with OGD requirements. Please refer to the completed Batch Inventory Control Sheets located on Pages 581, 655, and 735 of our original ANDA submission. Following standard practice, Zenith bases our packaging scheme on the container/closure configurations required for stability testing. These configurations consist of the smallest and largest package size within each container/closure system. For example, Labetalol Hydrochloride Tablets USP, 100 mg, Batch No. ND-242 was fully packaged in 100's/CRC, 100's/Non-CRC, and 1000's/Non-CRC. The 500's package size (500's/Non-CRC) is not necessary for stability

purposes because it is supported by the smallest (100's/Non-CRC) and largest (1000's/Non-CRC) packaging configurations, i.e. bracketing. This pertains to the 200 mg and 300 mg dosage strengths as well. Thus, by packaging the entirety of each batch into the smallest and largest package size within each container/closure system (the required stability configuration), we have met the requirement for complete packaging of batches as set forth in the Agency's Industry Letter dated November 8, 1991, as well as the Agency's Policy and Procedure Guide #41-95 dated February 8, 1995.

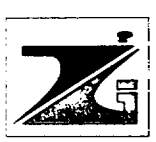
7. *Regarding finished product:*

   a. *The Certificate of Analysis for the finished product is incomplete. Batch size, date of manufacture, the source of active ingredient, manufacturing procedure (e.g., pilot or production batch), and manufacturing site should be included.*

Response:
For your review, we have revised the Certificates of Analysis for our exhibit batches ND-242 (100 mg), ND-241 (200 mg), and ND-243 (300 mg) to include the batch size, date of manufacture, source of active ingredient, manufacturing procedure, and manufacturing site. These can be found in Section 10 of this amendment. Please be advised that most of this information is considered proprietary, therefore, it is not routinely included in our Certificates of Analysis for finished product batches. Please note, however, that Zenith Goldline's batch numbering system has been designed to track this information. The batch number may be traced back to the master formula used, in which the batch size, date of manufacture, source of active ingredient, manufacturing procedure, and manufacturing site are specified. Information pertaining to our numbering system for production batches is contained in our original application under Section XVIII entitled, *"Control Numbers"*. To facilitate review, a copy of this procedure has been enclosed in Section 10 of this amendment.

   b. *The stability-indicating assay method submitted in Section XVI of the original submission is incomplete. Please submit in percentages the assay results of the active ingredient and degradation products under various stress conditions in tabular form.*

Response:
Please refer to Section 4 of this amendment, in which we have provided a report entitled, *"Modification to the USP Methods: Validation of the Stability Indicating Assay"*. Specifically, Part II of this report provides the tabulations requested by the Agency.



8. *Your application fails to submit satisfactory stability data. In this regard:*

   a. *Composition [see comments1.(a-c)] of the drug product must be included.*

   Response:
   We have revised the stability data section of our original application (Section XVII.4) to include the quantitative composition statement for each dosage strength. This information is located in Section 11 of this amendment. As instructed, the composition statement provided has been updated in accordance with Comments 1.(a-c); the remainder of the stability data section is unchanged and is identical to that which was submitted in our original ANDA filing.

   b. *Please provide more specific information regarding "Physical Evaluation" (e.g., color, odor, etc.).*

   Response:
   Zenith Goldline's specification for "Physical Evaluation" is defined as "free from physical defects (i.e., cracks, chips), discoloration, and uncharacteristic odor". Information pertaining to color is covered in the "Description" specification. Please understand that the stability data provided in our original application are issued reports, and, as such, cannot be changed. However, we acknowledge the Agency's request for more specific information regarding "Physical Evaluation", and have advised our Stability Department to revise the report forms accordingly in the future.

B. LABELING DEFICIENCIES

1. *CONTAINER*
   Please assure that the established name and strengths appear prominently on all labels. We encourage you to make a distinction among your various product strengths by using boxing and/or contrasting colors, or some other means.

   Response:
   Please be assured that it is our standard practice to differentiate product strengths by the use of contrasting colors in the boxes. However, the draft container labels are photocopies, therefore, the contrasting colors cannot be discerned. Please refer to Section 12 of this amendment, where we have included the final printed container labels which provide the contrasting colors in the boxes.

2. *INSERT*

   Revise insert as instructed in various Comments 2.a. - 2.d.

Please revise your labels and labeling, as instructed above, and submit in final print. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR §314.94(a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

Response:
Section 12 of this amendment contains final printed container labels and insert labeling which incorporate the changes specified by the Agency. In accordance with 21 CFR §314.94(a)(8)(iv), Section 12 also provides the required side-by-side comparison with our last submission, with all differences annotated and explained.

We acknowledge the Agency's right to request further changes to our labels and labeling based upon changes in the approved labeling of the listed drug, or upon further review of the application prior to approval.

This completes our Major Amendment response to the Agency's letter of July 3, 1996. We trust that all outstanding deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm D
Director,
Regulatory Affairs

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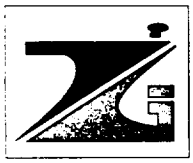
Enclosures



Zenith Goldline
PHARMACEUTICALS

Saundra Middleton
Cleared
12/1/95
11/30/95
Revised Letter

November 14, 1995

Charles Stanley, MD
Acting Director, Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
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GENERIC DRUGS

RE: ANDA: Labetalol Hydrochloride Tablets USP 100 mg, 200 mg and 300 mg

Dear Sir/ Madam:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, and 21 CFR §314.92 and §314.94, we are submitting an Abbreviated New Drug Application for Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg

PLEASE NOTE: Documents within this submission may refer to both Zenith Laboratories, Inc. and Zenith Goldline Pharmaceuticals. For clarification, Zenith Laboratories, Inc. is now a wholly-owned subsidiary of Zenith Goldline Pharmaceuticals. We are in the process of initiating a transfer of ownership of this ANDA from Zenith Laboratories, Inc. to Zenith Goldline Pharmaceuticals in accordance with 21 CFR 314.72.

The conditions of use, active ingredient, route of administration, dosage form, strength and labeling of the proposed product are the same as the reference listed drug specified in this application, **NORMODYNE®** 100 mg, 200 mg and 300 mg Tablets (Schering Corporation).

Section III of this application contains the required Patent Certification Statement and Marketing Exclusivity Information. In accordance with the Paragraph III Certification, it is Zenith's intent to introduce Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg following expiration of Patent 4,012,444, Lunts *et. al.*, (expiry August 2, 1998). The reference drug is no longer entitled to a period of marketing exclusivity under 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act. According to the information published in the "Orange" Book, the ten year "NCE" exclusivity expired on August 1, 1994.

The active ingredient used in the manufacture of Zenith's Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg, was manufactured by

(DMF DMF authorization reference, technical data and analytical methodologies are provided in Sections VIII and XVI of this application.

The following exhibit (test) batches in support of this application were manufactured and packaged at Zenith Laboratories, Northvale, NJ:

- ND 242 Labetalol Hydrochloride Tablets USP, 100 mg)
- ND 241 Labetalol Hydrochloride Tablets USP, 200 mg)
- ND 243 Labetalol Hydrochloride Tablets USP, 300 mg).

Upon approval and completion of validation, commercial batches, scaled-up in accordance to OGD Policy and Procedure Guide 22-90, will also be manufactured and packaged at our Northvale, NJ facility.

A certification statement, as required by the Generic Drug Enforcement Act of 1992, is provided directly following this letter. Additionally, a field copy certification statement is provided attesting that a true and accurate copy of the technical section of this application has been forwarded to our FDA District Office in accordance with 21 CFR §314.94(d)(5).

A Table of Contents precedes a signed Form FDA 356h which is included in Section I. The Archival Copy of this application, contained in blue jackets, consists of twelve (12) volumes, labeled inside as Volume 1 through Volume 12. Volumes 5 through 12 of this Archival Copy include the completed bioavailability studies.

The Review Copy is divided into two parts. The first part, contained in red jackets, consists of four (4) volumes, labeled inside as Volumes 1- 4, and includes the Chemistry, Manufacturing, and Controls Technical Section. The second part, contained in orange jackets, consists of eight (8) volumes labeled inside as Volume 5 through Volume 12, and includes the Bioavailability/Bioequivalence data.

In vivo bioavailability studies have been conducted comparing Zenith's Labetalol Hydrochloride Tablets USP, 200 mg (batch ND 241) to Schering's NORMODYNE® 200 mg tablets (Lot 94063). Both a fed and fasted study were conducted in support of this application. Although the reference listed drug for Labetalol HCl Tablets is the 300 mg strength, the bioavailability studies referenced in this application were conducted comparing the 200 mg strengths. The selection of the 200 mg strength is based on literature references which indicate that a single, 200 mg, oral dose produces acceptable reduction in blood pressure. As such, the medical monitor for our clinical studies was not willing to submit a 300 mg single dose study to the IRB due to the possibility of excessive blood pressure reductions. The diskette containing the bio-data is located on the inside front cover of the first volume (Volume 5) of the orange review copy of this application. A bioavailability

waiver request for Zenith's Labetalol HCl Tablets USP, 100 mg and 300 mg , filed in accordance to 21 CFR 320.22 (d)(2), is provided in Section VI of this application.

Please note that references to our physical facilities, production equipment, key personnel, and general operating procedures and controls, for the most part, have not been included in this application, in compliance with the OGD Policy and Procedure Guide No. 31-91, dated January 11, 1994, and restated in FDA Letter to Industry (All NDA, ANDA, and AADA Applicants) dated October 14, 1994. It is our understanding that this information will be reviewed by the local FDA District Office during their inspection process, and will not be requested by the reviewing chemists. In place of the above information, we are providing a brief, general description of our location, operation, and controls in Section IX, as well as appropriate summaries in other sections.

Two separately bound copies of the methods validation are also being submitted with this application.

Pursuant to Section 5 USC §552(b)(4) of the Freedom of Information Act of 21 CFR §20.61, regarding privileged and confidential information, we declare that information on Labetalol HCl Tablets USP, 100 mg, 200 mg and 300 mg, as to its composition, method of manufacture, and methods of testing constitute trade secrets and confidential commercial information under the law and are, therefore, not disclosable under the Freedom of Information Act.

We respectfully request a review of this application at your earliest convenience.

Sincerely,

ZENITH LABORATORIES, INC.

Robert J. Monaghan
Director, Regulatory Affairs